NATURALLY LUBRICATED SYSTEMS?

Abstract

Based on an experimentally observed behavior, a friction metaphor is suggested here as an explanatory mechanism of the clockwise hysteresis resulting when applying the drug Zstk to kidney cancer cells as a way to disrupt the AKT signaling pathway driving the proliferation state. The friction metaphor is based on some realized similarities between kinetic mechanical friction (as a result of the relative motion between two rigid surfaces in contact) and the responsive cellular behavior (resulting from the application of the Zstk drug). The metaphor friction suggest a possible connection between sustained oscillations manifested by a mathematical model of a reduced version of the AKT signaling pathway, and the dither process (virtual lubrication of mechanical systems via induction of vibrations). It is then suggested that some oscillatory behaviors in mechanical systems would be driving reactivity responses to environmental stimulus, which would allows to regard some biological systems as naturally lubricated systems.

1. Friction in mechanical systems

Friction is a common term in colloquial language essentially defining the kinetic force resisting the relative motion of two surfaces in contact (named dry friction if involving solid objects, and fluid friction if involving a solid and a gas or liquid). As an empirically observed phenomenon, friction (which converts kinetic energy into thermal energy) is a force derived from electromagnetic forces between atoms and electrons, being dry friction caused by chemical bonding between the surfaces in contact. This bonding is classically described in mechanical terms considering that the surfaces in relative motion are in contact through idealized bristles, which model the roughness of the surface. The friction force is then explained by tribology (the science of friction) practitioners by the effort needed to move two brushes relative to each other, with their bristles in contact. Using this analogy, the difference between static and kinetic friction could be explained by the fact that, at relatively higher speeds, the bristles may jump over gaps resulting in a less opposition to the motion. The reduction of friction due to lubrication could also be explained by lubricant filling up the gaps. As far as mathematical modeling of friction is concerned, the Dahl model captures the essence of the experimentally observed phenomenon, and specifically describes the clockwise (**CW**) hysteretical phenomenon experimentally observed (see Figure 1).

Since kinetic friction is frequently a source of degradation of the involved surfaces (*e.g.* friction tears the shoes up when walking), lubrication (*i.e.* the addition of a lubricator between the surfaces in relative motion) is a common mechanism to reduce the strength the friction force (it must be pointed out that not always friction is an undesired phenomenon, under certain conditions friction is even added to some classes of feedback-based controlled mechanical systems (servomechanisms for short) in order to stabilize them, see for instance [2] and the references therein). Lubrication is not necessarily a procedure involving a physical lubricator, as we explain in what follows.

2. Dithering as a mechanism to compensate friction

When considering lubrication, it can be performed by a physical procedure (just consisting in the addition of a lubricator between the surfaces in relative motion, *e.g.* some kind of oil in the case of metal surfaces) or a *virtual one* (though it is also a physical procedure). During the Second World War, engineers remarked that airplane autopilots (mechanical systems including gear trains) worked better in flying airplanes

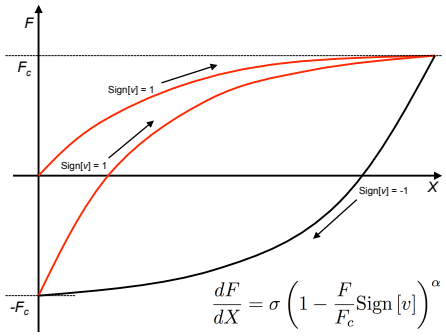


FIGURE 1. DAHL'S FRICTION MODEL. This figure shows the clockwise (**CW**) hysteresis which characterizes experimentally observed kinetic friction. F denotes the friction force, X denotes de relative motion between the two surfaces in contact, F_c denotes the Coulomb friction, σ is the stiffness coefficient, and α is a parameter that determines the shape of the stress-strain curve (the value $\alpha = 1$ is most commonly used). v denotes the velocity, and the arrow heads shows the direction of motion. As can bee seen in this model the friction is supposed to be only a function of the displacement and the sign of the velocity (which can be then understood a logical variable).

than in the design table on land, and they concluded that high frequency disturbing forces generated by the vibratory behavior of the airplane played the role of lubrication. Engineers installed then small motors in the autopilots to induce vibrations and consequently reduce friction, and it worked (see for instance [3]). In terms of the idealized bristles, the induced vibrations reduced the gap between them acting thus as a lubricator. This friction compensation mechanism is called *dither* (a word which comes from a British colloquialism for "undecidedness", or "wishy washiness") and it is in fact a very common procedure to improve precision in servomechanisms, like the one insuring the accuracy of the position of radiotelescope anthems (see for instance [1]). The dither concept is also applied in both audio and video engineering to avoid audio signals to be "not fluid" because of quantization error due to packing high resolution signals as low resolution ones (see for instance [4] and the references therein), and to produce digital halftoning in pictures coming from quantized visual signals (see [5] and [6]), respectively. As can be seen, friction is not a concept restricted to mechanical systems. In what follows we shall introduce some ideas concerning its application to the understanding of a dynamical behavior observed in a well-known cancer signaling pathway, when considering a drug targeting procedure.

3. THE HYSTERETICAL PHENOMENON IN CANCER MODIFIED SIGNALING PATHWAYS

When applying the Zstk drug to kidney cancer cells, the AKT signaling pathway is disrupted (the expression of the Pi3K is inhibited), which is translated in terms of the relation between the concentration of Zstk and nuclear FOXO1a, as shown in Figure 2. In both curves of this figure each point corresponds to the measured steady state of nuclear FOXO1a concentration for a given concentration of the Zstk drug, characterized via fluorescent-based microscopy of a genetically engineered set of inmortalized human kidney cells (the nucleus of the cells is marked by a histones-bound fluorescent dye) and the transcription factor FOXO1a is also marked with a fluorescent dye to match its evolution on time. The treated case corresponds to cells previously treated with Zstk, but which have been washed to eliminate the drug. As can be seen when comparing Figure 2 with Figure 1, the FOXO1a-Zstk relation shows **CW** hysteresis.

In words, the cells treated with Zstk *remember* it after being washed. In fact hysteresis describes a memory-induced phenomenon (in the case of ferromagnetic memory devices used in digital computers, counter clockwise (**CCW**) hysteresis rules the recording process). Following the friction concept in metaphorical terms, the Zstk concentration can be interpreted as the displacement, while the concentration of the nuclear

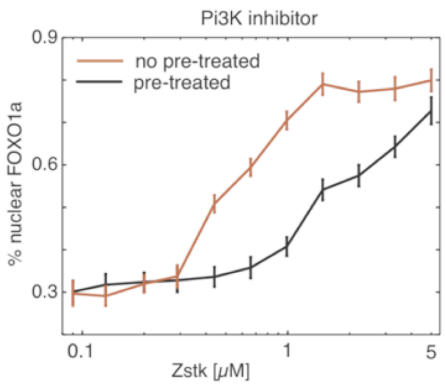


FIGURE 2. **CW** HYSTERESIS IN THE FOXO1A-ZSTK RELATION. This image shows the behavior observed experimentally when disrupting the AKT signaling pathway through the application of the Zstk drug, in two different cases: the non-pretreated case (in red) and the treated case (in black).

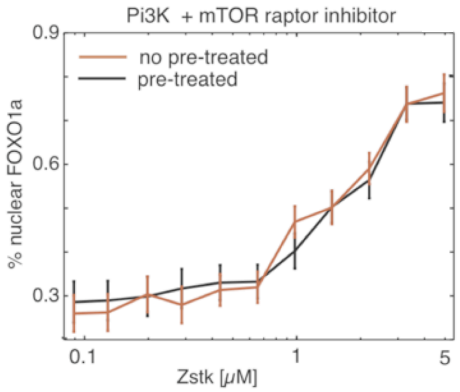


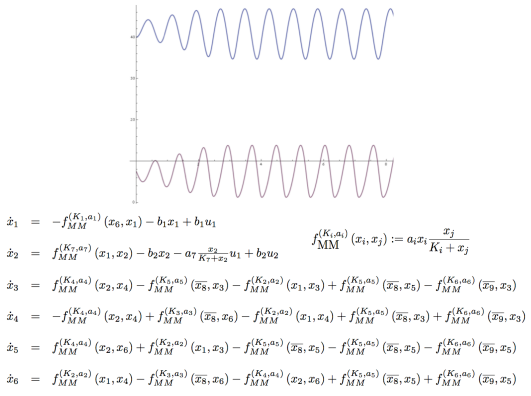
FIGURE 3. DISAPPEARING HYSTERESIS INHIBITING MTOR RAPTOR. The figure shows the experimentally observed FOXO1a-Zstk relation when the treated cells are modified in order to suppress the expression of mTOR raptor.

FOXO1a can me interpreted as the resulting friction force, which in this case is the *desired* consequence of the application of Zskt (since the presence of FOXO1a in the nucleus of the cells means that the cellular proliferation state is stopped). When adding a mTOR raptor inhibitor to the cells treated by Zstk hysteresis disappear, *i.e.* there is no significant difference between the treated and the non-treated cases (see Figure 3). Note that the level of the measured steady state of FOXO1a, for a given concentration of Zstk, is reduced (when comparing with the corresponding level observed in the non-treated case as depicted in the red curve in Figure 2). In terms of the proposed friction metaphor, the inhibition of mTOR raptor acts as the addition of a lubricator, reducing then the friction force (*i.e.* the level of nuclear FOXO1a). In this case Zstk is less effective.

4. IS THERE DITHER IN THE SIGNALING PATHWAY?

When considering the experimental results through the friction metaphor, it is a logical consequence to ask about the possible presence of a like-dither process in the signaling pathway. The immortalized kidney cells suffers from the disruption of its AKT signaling pathway, which promotes cellular proliferation, and the application of the reversible drug Zstk stops this undesired phenomenon, while the supplementary addition of a mTOR inhibitor makes **CW** hysteresis unobservable. If friction was not present (which is to say if the level of nuclear FOXO1a was zero), it would suggests the presence of lubrication. Since Zstk works via the inhibition of Pi3K, this protein would be mastering a like-dither process (always in terms of the friction metaphor). When considering a nonlinear differential equation model of a reduced version of the AKT signaling pathway, concerning the behavior of the cellular concentrations of the proteins mTOR rictor, PDK1p, AKTp, AKT, pAKT, pAKTp, and pAKT (mTOR raptor is modeled as the difference between the initially available mTOR raptor protein and the rictor one), sustained oscillations appears, as shown in Figure 4, for the parameters and initial conditions shown in Table 1.

Since the oscillations displayed by the simulated dynamics are high-frequency ones, it would very hard to check if this property of the model corresponds to real sustained oscillations in the



$$
\begin{aligned}
\dot{x}_1 &= -f_{MM}^{(K_1,a_1)}(x_6,x_1) - b_1x_1 + b_1u_1 \\
\dot{x}_2 &= f_{MM}^{(K_7,a_7)}(x_1,x_2) - b_2x_2 - a_7\tfrac{x_2}{K_7+x_2}u_1 + b_2u_2 \qquad f_{\mathrm{MM}}^{(K_i,a_i)}(x_i,x_j) := a_ix_i\tfrac{x_j}{K_i+x_j} \\
\dot{x}_3 &= f_{MM}^{(K_4,a_4)}(x_2,x_4) - f_{MM}^{(K_5,a_5)}(\overline{x_8},x_3) - f_{MM}^{(K_2,a_2)}(x_1,x_3) + f_{MM}^{(K_3,a_3)}(\overline{x_8},x_5) - f_{MM}^{(K_6,a_6)}(\overline{x_9},x_3) \\
\dot{x}_4 &= -f_{MM}^{(K_4,a_4)}(x_2,x_4) + f_{MM}^{(K_3,a_3)}(\overline{x_8},x_6) - f_{MM}^{(K_2,a_2)}(x_1,x_4) + f_{MM}^{(K_3,a_5)}(\overline{x_8},x_3) + f_{MM}^{(K_6,a_6)}(\overline{x_9},x_3) \\
\dot{x}_5 &= f_{MM}^{(K_4,a_4)}(x_2,x_6) + f_{MM}^{(K_2,a_2)}(x_1,x_3) - f_{MM}^{(K_5,a_5)}(\overline{x_8},x_5) - f_{MM}^{(K_3,a_3)}(\overline{x_8},x_5) - f_{MM}^{(K_6,a_6)}(\overline{x_9},x_5) \\
\dot{x}_6 &= f_{MM}^{(K_2,a_2)}(x_1,x_4) - f_{MM}^{(K_3,a_3)}(\overline{x_8},x_6) - f_{MM}^{(K_1,a_1)}(x_2,x_6) + f_{MM}^{(K_3,a_5)}(\overline{x_8},x_5) + f_{MM}^{(K_6,a_6)}(\overline{x_9},x_5)
\end{aligned}
$$

FIGURE 4. SUSTAINED OSCILLATION IN THE AKT SIGNALING PATHWAY. This figure shows the oscillatory behavior of the cellular concentrations of rictor (in blue) and active AKT (*i.e.* pAKTp, in red).

name	quantity	value or in. cond.
a_1	$\alpha_{\text{pAKT\_rictor}}$	10
a_2	$\alpha_{\text{rictor\_AKT}}$	20
a_3	$\alpha_{\text{PP2A\_pAKT}}$	4
a_4	$\alpha_{\text{PDK1p\_AKT}}$	20
a_5	$\alpha_{\text{PP2A\_AKTp}}$	1
a_6	$\alpha_{\text{PTEN\_AKTp}}$	1
a_7	$\alpha_{\text{raptor\_PDK1p}}$	10
x_1	$[rictor]$	0.0
x_2	[PDK1p]	50.0
x_3	$[AKTp]$	0.0
x_4	$[AKT]$	100.0
x_5	$[pAKTp]$	0.0
x_6	$[pAKT]$	0.0
K_1	$K_{\text{pAKT\_rictor}}$	10
K_2	$K_{\text{rictor\_AKT}}$	5.0
K_3	$K_{\text{PP2A\_pAKT}}$	0.1
K_4	$K_{\text{PDK1p\_AKT}}$	10.0
K_5	$K_{\text{PP2A\_AKTp}}$	0.1
K_6	$K_{\text{PTEN\_AKTp}}$	0.25
K_7	$K_{\text{raptor\_PDK1p}}$	10.0
$\overline{x_8}$	$[PP2A]$	150.0
$\overline{x_9}$	$[PTEN]$	200.0
u_1	mTOR_total	100.0
u_2	PDK1_total	100.0
b_1	$\beta_{\text{raptor\_2\_rictor}}$	1.0
b_2	$\beta_{\text{PDK1\_2\_PDK1p}}$	5.0

TABLE 1. Parameters and initial conditions for the simulation shown in Figure 4.

signaling pathway. Perhaps the oscillatory behavior is only a model artifact. However, the question deserves to be addressed. When considering the observed hysteretical behavior, it must be pointed out that the considered Dahl model assumes that between the surfaces in relative motion the contact is due to the presence of idealized bristles (considered as a sort of springs), and hysteresis is explained in terms of change of the elastic properties of the bristles. If the idealized bristles were oscillating, the hysteretical behavior would be attenuated. Thus, hysteresis would appear when applying Zstk because the sustained oscillations of the non manipulated signaling pathway are damped. Inhibition of mTOR raptor would then reestablish the underlying dither process.

5. SOME CONCLUDING REMARKS

Since biological systems are nonlinear dynamic systems, they are able to exhibit sustained oscillations (see for instance [7] and [8], and the references therein), which are frequently related to the synchronization of cellular activities with environmental rhythms (*e.g.* circadian cycles) or intracellular communication. This behavior is generally driven by the interplay of collaborative and competitive feedback loops ruling the regulatory cellular networks. However, experience proved that similar properties emerges in natural and artificial systems (like modularity, see for instance [9]). As was pointed out previously, concepts like dither, originated in the study of friction in mechanical systems, has found its place in some other engineering domains. The experimental results that motivates this paper, as well as the ability of the mathematical model of the reduced AKT signaling pathway, suggest that like-dither processes may be also present in biomolecular systems. In fact, phenomena like friction and hysteresis, related to underlied by oscillatory disturbances, have been described in the molecular mechanisms driven the behavior of force length and force calcium relations in muscles (see [10]). The friction metaphor suggest that oscillatory behaviors may be not only a mechanism involved in synchronization and communication, but also a mechanism driving reactivity responses, which is

of particular interest when considering drug targeting strategies.

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